201-15166A

High Production Volume (HPV) Challenge Program

Benzenemethanethiol
CAS Number 100-53-8

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ABBREVIATIONS

BCF = predicted bioconcentration factor
Benzenemethanethiol = Benzyl Mercaptan
BZM = Benzyl Mercaptan
cm^3 = cubic centimeter
CPChem = Chevron Phillips Chemical Company LP
CSI-Closed System Intermediate
gd = gestation day
H_2S = hydrogen sulfide
hPa = hectopascal
HPV = High Production Volume
IUCLID = International Uniform Chemical Information Dataset
Koc = organic carbon partition coefficients
LC_{50} = lethal concentration (to 50% of animals dosed)
LD_{50} = lethal dose (to 50% of animals dosed)
LOAEL = lowest observed adverse effect level
mg/kg = milligram per kilogram
mg/L = milligrams per liter
mmHg = millimeter mercury
NaSH = sodium hydrosulfide
NOAEL = no observed adverse effect level
OECD = Organisation for Economic Cooperation and Development
PHM = Phenyl Mercaptan
QSAR = Quantitative Structure Activity Relationship
RACB = Reproductive Assessment by Continuous Breeding
SIDS = Screening Information Data Set
USEPA = United States Environmental Protection Agency
USFDA = United States Food and Drug Administration

I. EXECUTIVE SUMMARY

Chevron Phillips Chemical Company LP (CPChem) is committed to fulfilling the High Production Volume (HPV) commitments it made under the United States Environmental Protection Agency (USEPA) HPV Challenge Program on February 14, 2001. As part of this commitment, CPChem has volunteered to assess the health and environmental hazards, including selected physicochemical characteristics of Benzenemethanethiol (CASN 100-53-8), commonly known as and referred to hereafter as Benzyl Mercaptan (BZM). BZM is a member of the broader family of organomercaptans, which are characterized by their very strong malodor and low odor threshold. CPChem currently manufactures BZM for use as a raw material in the production of agricultural pesticide ingredients.

CPChem has identified data from company proprietary files, peer-reviewed literature, and/or calculated endpoints using widely accepted computer modeling programs. In fulfillment with USEPA guidance for use of read-across data (USEPA, 1999b), CPChem proposes the use of surrogate data from Phenyl Mercaptan (CASN 108-98-5) (PHM), a close structural analogue to BZM, to fill Screening Information Data Set (SIDS) endpoint data gaps and provide additional support in our understanding of health and environmental hazards for BZM. Both BZM and PHM have a relatively narrow range of physicochemical parameters and are composed of similar functional groups. Thus, these two substances are expected to demonstrate similar environmental fate and toxicological profiles.

Physicochemical endpoints for BZM are fulfilled by using existing measured data or data calculated by the EPIWIN© computer model. No additional testing is proposed for this program.

An estimation from a Level III fugacity model predicts that BZM and PHM will likely partition to soil and water. Ready biodegradation testing showed that BZM is not readily biodegradable. The predicted bioconcentration factors and organic carbon partition coefficients for BZM and PHM suggest similar fate profiles in the environment and no bioaccumulation hazard for either BZM or PHM. A review of the existing data for BZM and PHM shows that sufficient data are available to characterize the environmental fate of BZM, with the exception of the Hydrolysis SIDS endpoint. Additional testing for the Hydrolysis SIDS endpoint is therefore proposed for this program.

A review of the existing data for BZM and PHM shows that insufficient data are available to characterize aquatic toxicity. Additional testing for the Acute Toxicity to Fish and Aquatic Plants (Algae) endpoint is proposed for this program.

A limited amount of existing mammalian toxicity information on BZM and PHM demonstrates that PHM is a conservative read across benchmark, with slightly higher toxicity than BZM. Acute toxicity studies show that BZM is of low acute toxicity by oral, inhalation, dermal, and intraperitoneal routes. BZM has not been tested for reproductive toxicity; reproductive toxicity data are available for PHM. Due to its close

structural similarity to PHM, as well as the demonstrated higher level of acute toxicity of PHM, it would be expected that BZM would be of a similar order of magnitude as PHM, if not of lower reproductive toxicity. Repeated dose toxicity testing has not been performed on BZM or PHM; therefore, repeated dose toxicity testing is proposed. Likewise, no *in vitro* chromosomal aberration studies were identified for either BZM or PHM. As a result, testing is proposed to meet the chromosomal aberration requirements. BZM has not been tested for developmental toxicity; however data is available for PHM. Due to its close structural similarity to PHM, as well as the demonstrated higher level of acute toxicity of PHM, it would be expected that BZM would be of a similar order of magnitude as PHM, if not of lower developmental toxicity.

Nearly all HPV endpoints have been satisfied for BZM. The close structural surrogate PHM serves as a read-across for some endpoints (as described below). PHM surrogate data are available for several HPV endpoints. Table 1 summarizes the available data for BZM and PHM.

Table 1. Matrix of Available and Adequate Data on BZM and PHM

Test	BZM Y/N (Klimish Score)	PHM Y/N (Klimish Score)	Testing Planned? Y/N
Physical and Chemical Data			
Melting Point	Y (2)	Y (2)	N
Boiling Point	Y (2)	Y (2)	N
Vapor Pressure	Y (2)	Y (2)	N
Partition Coefficient	Y (2)	Y (2)	N
Water Solubility	Y (2)	Y (2)	N
Environmental Fate and Pathways			
Photodegradation	Y (2)	Y (2)	N
Stability in Water (Hydrolysis)	N	N	Y
Transport/Distribution	Y (2)	Y (2)	N
Biodegradation	Y (2)	N	N
Ecotoxicity			
Acute/Prolonged Toxicity to Fish	N	N	Y
Acute Toxicity to Aquatic Invertebrates (*Daphnia*)	Y (1)	N	N
Acute Toxicity to Aquatic Plants (Algae)	N	N	Y
Toxicity			
Acute Toxicity (Oral)	Y (2)	Y (2)	N
Acute Toxicity (Inhalation)	Y (2)	Y (2)	N
Acute Toxicity (Dermal)	Y (1)	Y (2)	N
Repeated Dose	N	N	Y
GeneticToxicity *in vitro* – Gene Mutation	Y (2)	N	N
Genetic Toxicity – Chromosomal Aberration	N	N	Y
Reproductive Toxicity	N	Y (1)	N
Developmental Toxicity	N	Y (1)	N

Note: *The data used to characterize the OECD SIDS endpoints for substances in this Test Plan were identified either in company proprietary files, peer-reviewed literature, and/or calculated using widely accepted computer modeling programs. PHM was used for read-across as defined by the USEPA (1999b). All data were evaluated for study reliability in accordance with criteria outlined by the USEPA (1999a). Only studies that met the reliability criteria of "1" (reliable without restrictions) or "2" (reliable with restrictions) were used to fulfill OECD SIDS endpoints. Additional data for BZM and PHM are also included in the IUCLID (International Uniform Chemical Information Dataset) attached in Appendices I and II. A more detailed discussion of the data quality and reliability assessment process used to develop this test plan is provided in Appendix III.*

Summary: Adequate data (i.e., Klimisch rating 1 and 2) are available for all endpoints except Hydrolysis, Acute Toxicity to Fish, Acute Toxicity to Aquatic Plants, Repeated Dose, and Genetic Toxicity: *In vitro* Mammalian Cytogenetic Test. Additional testing with BZM is proposed to fulfill these six endpoints.

II. GENERAL SUBSTANCE INFORMATION

BZM is a member of the broader family of organomercaptans, which are also sometimes referred to as thiols or sulfhydryls. Many are naturally occurring and are characterized by their very strong malodor and low odor threshold (~1 ppb), a property that creates an immediate odor nuisance while keeping exposure and potential for adverse effects to humans at a minimum.

Today, CPChem is the major US producer of BZM, *and* CPChem annual production volumes are sold to one client. BZM is manufactured and transported in a closed system process and used as a chemical intermediate to produce agricultural pesticides, also in a closed system process. Traces or residues of BZM in end products are negligible as ppb amounts would introduce a malodor.

CPChem originally prepared documentation to substantiate that BZM is a closed system intermediate (CSI) pursuant to the USEPA's guidance for closed system intermediates for the HPV Challenge Program. However, CPChem dropped this approach based on the following two factors:

- It is unlikely the USEPA and the international community will accept closed system intermediate status and a reduced test package for BZM because CPChem's processing of BZM in the US is not site limited. The BZM is transported by railcar to another site, where it is a chemical intermediate in the production of agricultural pesticides.

- BZM is also approved by U.S. Food and Drug Administration (FDA) as a food additive. This is suggestive that specialty chemical distributors marketing natural BZM for this application may exist.

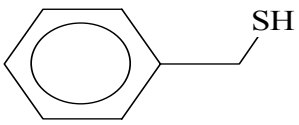
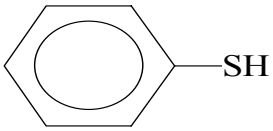
BZM CSI processes are confidential business information, but are available upon request for further evaluation by USEPA.

III. STRUCTURAL SURROGATE DISCUSSION

Because a substantial amount of data exists for BZM, it is possible to characterize several of the OECD SIDS hazard endpoints and to meet the requirements of the USEPA HPV Challenge Program. However, PHM also serves as a close structural surrogate to BZM and adds to the weight of evidence in characterizing many BZM physical/chemical, environmental, and human health-related endpoints.

Figure 1 presents the chemical structures for BZM and PHM. These substances are close structural analogs having the same functional groups. They differ only in the presence in BZM of a methylene group between the aromatic ring and the thiol group, which results in a difference in molecular weight of only 14 atomic mass units. The following sections illustrate that these surrogates have similar physical, chemical, environmental fate and effects, and toxicological properties. Given that PHM is slightly lower in molecular weight, it is slightly more water soluble, mobile, and bioavailable, making it a conservative read across benchmark with slightly higher toxicity than BZM. This is important because the trend is consistent and shows that where there are BZM data gaps, and PHM data are available for read-across purposes, additional testing on BZM will not provide new useful data.

Figure 1. Structural Comparison of Benzenemethanethiol and Benzenethiol

US HPV Chemical **Benzenemethanethiol** **(Benzyl Mercaptan / BZM)**	**Structural Surrogate** **Benzenethiol** **(Phenyl Mercaptan / PHM)**
	
CAS Number - 100-53-8 Molecular Weight = 124.20 SMILES: Scc (cccc1) c1	CAS Number - 108-98-5 Molecular Weight = 110.17 SMILES: Sc (cccc1) c1

IV. PHYSICOCHEMICAL PROPERTIES

The physical chemical data for BZM and PHM provided in Table 2 were experimentally confirmed or primarily obtained from well-established and scientifically accepted reference handbooks such as the Merck Index (O'Neil, 2001), Patty's Industrial Hygiene and Toxicology (Bingham, 2001), Sax's Dangerous Properties of Industrial Materials (Lewis, 2000), and the CRC Handbook of Chemistry and Physics (Lide, 2001-2002), as

well as EPIWIN-calculated values (USEPA and Syracuse Research Corporation, 2000). These data show that both BZM and PHM are moderately water soluble and have similar melting and boiling points, vapor pressure, and hydrophobicity (log Kow).

Table 2. Measured (M) and Calculated (C) Physicochemical Properties

Physical and Chemical Data				
Test	**M/C**	**BZM**	**M/C**	**PHM**
Melting Point	M[1] C[2]	-30 ºC -19.22 ºC	M[3,4] M[1] C[2]	-14.8 to -14.9 ºC -14.9 ºC -31.86 ºC
Boiling Point	M[4,5] M[1] C[2]	194-195 ºC 194.5 ºC 200.14 ºC	M[3,4,6] M[1] C[2]	168.7 to 169.5 ºC 169.1 ºC 176.14 ºC
Vapor Pressure	C[2]	0.474 mmHg (0.632 hPa)	M[4] M[1] C[2]	2.67 hPa at 25 ºC 1.93 mmHg (2.57 hPa) 1.63 mmHg (2.17316 hPa)
Kow Partition Coefficient	C[7]	2.48	M[8] M[1] C[7]	2.52 2.52 2.69
Water Solubility	C[9]	732.2 mg/L (at 25 ºC)	M[3] M[1] C[9]	1 at 25 ºC 835 mg/L (at 25 ºC) 765.5 mg/L (at 25 ºC)

[1] EPIWIN v3.10; measured values from the EPIWIN experimental database.
[2] EPIWIN v3.10; calculated using MPBPWIN v1.40 (determined at 760 millimeter mercury [mmHg]).
[3] Lide, 2001-2002.
[4] Bingham, 2001.
[5] O'Neil, 2001.
[6] Lewis, 2000.
[7] EPIWIN v3.10; calculated using KOWWIN v1.66.
[8] Sangster, 1989.
[9] EPIWIN v3.10; calculated using WSKOW v1.40.

Summary: Adequate data (i.e., Klimish rating 1 and 2) are available for all endpoints; no additional testing is proposed for the USEPA HPV Challenge Program (see Table 2 and IUCLID documents).

V. EVALUATION OF ENVIRONMENTAL FATE DATA

Environmental fate data for BZM and PHM were either experimentally measured or estimated using EPIWIN, and are provided in Tables 3, 3a, and 3b. Overall, these substances are expected to be mobile if released to the environment, but they will ultimately degrade based upon both biotic and abiotic degradation mechanisms and do not pose any bioaccumulation hazard.

Table 3. Results for Environmental Fate and Pathways

Environmental Fate and Pathways				
Test	**M/C**	**BZM**	**M/C**	**PHM**
Photodegradation & Atmospheric Oxidation: • OH Rate Constant • OH Half Life	 C[1] C[1]	 44.63 x 10^{-12} cm^3/molecule-sec 2.876 Hrs	 C[1] C[1]	 11.32 x 10^{-12} cm^3/molecule-sec 11.34 Hrs
Stability in Water (Hydrolysis)		No Data Available		No Data Available
Transport/ Distribution • Fugacity • Estimated Koc: • Estimated BCF:	 C[2] C[3]	 See model results below (Table 3a) 518 16.32	 C[2] C[3]	 See model results below (Table 3b) 268 17.39
Biodegradation	M[4]	40.7% in 28 days (Closed Bottle - OECD 301d)		No Data Available

[1]EPIWIN v3.10; calculated using AOP Program v1.40.
[2]EPIWIN v3.10; calculated using PCKOC Program v1.66.
[3]EPIWIN v3.10; calculated using BCF Program v2.14.
[4] Elf Atochem S.A. Benzyl mercaptan,determination de la biodegradabilite facile,essai en fioles fermees.centre d'application de levallois,le 11/09/96

A. Photodegradation – Atmospheric Oxidation

Values for BZM photodegradation and atmospheric oxidation were calculated based upon chemical structures using EPIWIN and are shown in Table 3. A calculated half-life for BZM of 2.876 hours and rate constant of 44.63 x 10^{-12} cubic centimeter (cm^3)/molecule-sec has been estimated for reaction with hydroxyradicals, compared to a calculated half-life for PHM of 11.34 hours and a rate constant of 11.32 x 10^{-12} cm^3/molecule-sec.

Summary: These results are sufficient for USEPA HPV Challenge Program, and no further testing is warranted.

B. Hydrolysis

BZM and PHM are both water soluble and are expected to be stable in water at environmentally relevant pHs. EPIWIN was unable to calculate a hydrolysis rate constant for either structure due to the absence of functional groups that are labile to hydrolysis.

Summary: Testing for Stability in Water (OECD Test Guideline 111) is recommended for BZM to fulfill this endpoint.

C. Chemical Transport and Distribution in the Environment (Fugacity Modeling)

Tables 3a and 3b summarize the Level III Fugacity results for BZM and PHM produced by EPIWIN.

Table 3a. EPIWIN Level III Fugacity Results for BZM

Compartment	100% to air	100% to water	100% to soil	Equally to each compartment
Air	92.6%	0.87%	0.22%	1.54%
Water	6.13%	98.6%	1.85%	36.0%
Soil	1.2%	0.01%	97.9%	62.3%
Sediment	0.03%	0.51%	0.01%	0.19%

Table 3b. EPIWIN Level III Fugacity Results for PHM

Compartment	100% to air	100% to water	100% to soil	Equally to each compartment
Air	94.4%	3.43%	1.01%	5.37%
Water	4.58%	96.0%	1.61%	34.2%
Soil	0.99%	0.04%	97.4%	60.3%
Sediment	0.03%	0.52%	0.01%	0.19%

Summary: Results from the Level III fugacity modeling indicate that releases to water would remain in water while releases to air and soil would partition to water and soil. These results also show that both compounds behave similarly in the environment and that further fugacity modeling is not warranted.

D. Biodegradation and Bioaccumulation

BZM has been tested in a Ready Biodegradation test, and the results are reliable without restrictions and fulfill the HPV SIDS endpoint for BZM. The results are also in agreement with EPIWIN calculated results. BZM should be inherently biodegradable under real-world aerobic and anaerobic conditions. However, under the conservative conditions of the standard OECD ready tests, BZM was shown not to be readily biodegradable.

The EPIWIN predicted bioconcentration factor (BCF) and organic carbon partition coefficients (Koc) are similar for BZM and PHM, suggesting that both are nonsorptive in the environment and pose no bioaccumulation hazard.

Summary: These results are sufficient for USEPA HPV Challenge Program purposes, and no further testing is warranted (See Table 3 and IUCLID Documents).

Environmental Fate and Pathways Summary: Adequate data (i.e., Klimisch rating 1 and 2) are available for all environmental fate endpoints with the exception of Stability in Water (Hydrolysis), for which testing is proposed consistent with OECD Test Guideline 111.

VI. ECOTOXICITY DATA

Table 4 shows that only limited experimental aquatic toxicity testing of BZM and PHM has been conducted. One aquatic study was performed on aquatic invertebrates (*Daphnia*). However, within EPIWIN, the ECOSAR module recognizes BZM as a member of both the Neutral Organic and Thiols (or Mercaptan) chemical classes and recognizes PHM as a member of both the Neutral Organic and Phenols chemical classes. ECOSAR has validated fish Quantitative Structure Activity Relationship (QSAR) and *Daphnia* acute toxicity endpoints for these classes that add perspective, but clear trends are not evident.

Table 4. Results for Ecotoxicity Endpoints

Ecotoxicity		
Test	**BZM**	**PHM**
AcuteToxicity to Fish	96-hr LC_{50} = 64 mg/L[1] 96-hr LC_{50} = 0.920 mg/L[2]	96-hr LC_{50} = 37 mg/L[1] 96-hr LC_{50} = 6.082 mg/L[3]
Acute Toxicity to Aquatic Invertebrates (Daphnid)	24 hr EC_{50} > 0.26 mg/L[4] 48 hr EC_{50} = 0.15 mg/L[4] 48-hr EC_{50} = 0.045 mg/L[2]	48-hr EC_{50} = 3.097 mg/L[3]
Acute Toxicity to Aquatic Plants (Algae)	No Data Available	96-hr EC_{50} = 13.4 mg/L[3]

[1] EPIWIN v3.10; calculated using ECOSAR Program for neutral organic chemicals.
[2] EPIWIN v3.10; calculated using ECOSAR Program for mercaptans.
[3] EPIWIN v3.10; calculated using ECOSAR Program for phenols.
[4] Elf Atochem S.A. 1997.

Ecotoxicity Summary: Sufficient data is available to warrant no further acute toxicity testing with aquatic invertebrates. Additional testing is proposed (OECD Guidelines 203 and 201) to meet the Acute Fish and Acute Aquatic Plants (Algae) HPV SIDS endpoints.

VII. MAMMALIAN TOXICITY

A limited amount of existing mammalian toxicity information on BZM and PHM demonstrates that PHM is a conservative read across benchmark, with slightly higher toxicity than BZM. The increased toxicity of PHM is likely due to its physicochemical characteristics; PHM has a slightly lower molecular weight, and is slightly more water soluble, mobile, and bioavailable than BZM. This is important because the trend is consistent and shows that where there are BZM data gaps in mammalian toxicity information, and PHM data are available for read-across purposes, additional testing on BZM will not provide new useful data.

Table 5. Results for Mammalian Toxicity Endpoints

Mammalian Toxicity		
Test	**BZM**	**PHM**
Acute Oral	LD_{50} 1 day = 985 mg/kg[1] LD_{50} 15 day = 493 mg/kg[1]	LD_{50} = 46.2 mg/kg[1]
Acute Inhalation	A. Rat LC_{50}: not calculable (one death out of 6 rats at 185 ppm and one death out of 6 rats at 235 ppm.[1] B. Mouse LC_{50} (24 hr): 195 ppm[1] Mouse LC_{50} (15 day): 178 ppm[1]	A. Rat LC_{50} (48 hr): 59 ppm[1] Rat LC_{50} (15 day): 33 ppm[1] B. Mouse LC_{50} (24 hr): 47 ppm[1] Mouse LC_{50} (48 hr): 35.5 ppm[1] Mouse LC_{50} (15 day): 28 ppm[1]
Acute Dermal	Rat LD_0: ≥ 2000 mg/kg[2]	Rat LD_{50}: 300 mg/kg[1]
Acute (i.p.)	LD_{50} 1 day = 429 mg/kg[1] LD_{50} 15 day = 373 mg/kg[1]	LD_{50} 1 day = 25.2 mg/kg[1] LD_{50} 15 day = 9.8 mg/kg[1]
Repeated Dose	No Data Available	No Data Available
Reproduction Toxicity	No Data Available	Reproductive toxicant both in males (based on increased incidence of inhibited spermiation in all treated F_1 males, and decreased epididymal sperm motility in the mid- and high dose [18 and 35 mg/kg] F_0 males) and in females (developmental -- based on decreased pup weights).[3]
Developmental Toxicity	No Data Available	A. Rat Maternal LOAEL: 20 mg/kg/day[4]; Rat Fetal NOAEL: 20 mg/kg/day[4] B. Rabbit Maternal NOAEL: 10 mg/kg/day[5]; Rabbit Fetal NOAEL: 40 mg/kg/day[5]
Genetic – Gene Mutation	Negative[6]	No Data Available

Mammalian Toxicity		
Test	**BZM**	**PHM**
Genetic – Chromosomal Aberration	No Data Available	No Data Available

[1] Fairchild and Stokinger, 1958.
[2] Centre International de Toxicologie, 1996.
[3] National Toxicology Program, 1996.
[4] National Toxicology Program, 1994a.
[5] National Toxicology Program, 1994b.
[6] Wild et al., 1983.
LOAEL = lowest observed adverse effect level.
NOAEL = no observed adverse effect level.

A. Acute Toxicity

Acute toxicity studies show that BZM is of low acute toxicity by the oral, inhalation, dermal, and interperitoneal routes (see Table 5 and IUCLID documents). Importantly, the close structural analogue PHM was also tested and consistently shows higher acute toxicity than BZM.

Summary: These studies fulfill the HPV requirements for the acute toxicity endpoint; no additional testing is proposed for the USEPA HPV Challenge Program.

B. Repeated Dose Toxicity

No repeated dose toxicity studies were identified for either BZM or its structural surrogate, PHM. As discussed in other sections, BZM will not be considered a closed system intermediate and therefore testing for this endpoint is proposed.

Summary: Additional testing is proposed for this endpoint consistent with OECD Guideline 407 (Repeated Dose 28-day Oral Toxicity Study in Rodents).

C. Genetic Toxicity/Mutagenicity

A valid *in vitro* gene mutation study (*Salmonella typhimurium* Reverse Mutation Assay) was performed for BZM and showed no mutagenic activity. No *in vitro* chromosomal aberration studies were identified for either BZM or PHM. The USEPA requires two different endpoints to be tested: gene mutation and chromosomal aberration. As a result, testing is proposed to meet the chromosomal aberration requirements.

Summary: Additional testing is proposed for this endpoint consistent with OECD Guideline 473 (Genetic Toxicology: *In vitro* Mammalian Cytogenetic Test) in order to meet the chromosomal aberration endpoint requirements.

D. Reproductive Toxicity

BZM has not been tested for reproductive toxicity. However, due to its close structural similarity to PHM, as well as the demonstrated higher level of acute toxicity of PHM, it would be expected that BZM would be of a similar order of magnitude as PHM, if not of lower reproductive toxicity. As a result, data for the structural surrogate PHM can be used as read-across data for BZM, and no further testing of BZM is warranted for this endpoint (see Table 5 and IUCLID Documents).

PHM was tested by the National Toxicology Program (1996) for reproductive toxicity in rats. This study followed the National Toxicology Program's Reproductive Assessment by Continuous Breeding (RACB) protocol and was found to be valid without restriction. PHM was determined to be a slight reproductive toxicant both in males (based on increased incidence of inhibited spermiation in all treated F_1 males, and decreased epididymal sperm motility in the mid- and high dose [18 and 35 mg/kg] F_0 males) and in females (developmental – based on decreased pup weights). Results of this study also show that PHM is not a selective reproductive toxicant because the minor effects on reproduction occurred concomitant with, or at doses greater than, those doses that produce hepatic or renal toxicity.

Summary*:* Adequate data (i.e., Klimisch rating 1) are available for this endpoint. Data for the structural surrogate PHM can be used as read-across data for BZM, and no further testing of BZM is warranted for this endpoint (see Table 5 and IUCLID Documents).

E. Developmental Toxicity

PHM was tested by the National Toxicology Program (1994a; 1994b) for developmental toxicity in both rats and rabbits. These studies followed OECD Guideline 414 and were found to be valid without restriction (Klimisch 1). In rats, the maternal LOAEL was 20 mg/kg/day, and the fetal NOAEL was 20 mg/kg/day. Maternal toxicity (observed as maternal mortality), a persistent decrease in body weight and weight gain, and a decrease in food consumption during the treatment period occurred at the high-dose level of 50 mg/kg/day. The LOAEL (20 mg/kg/day) for maternal toxicity was based on minor, transient decreases in maternal weight gain and food consumption on gestation day (gd) 6 to 9. The maternal NOAEL could not be determined based upon the doses evaluated. Developmental toxicity, observed as increased post-implantation death, decreased litter size, decreased fetal body weight, and an increase in the incidence of external malformations, occurred only at the high dose. Reduced female fetal body weight was observed at 35 mg/kg/day, suggesting an NOAEL of 20 mg/kg/day.

In rabbits, the maternal NOAEL was 10 mg/kg/day, and the fetal NOAEL was 40 mg/kg/day. The 40 mg/kg/day PHM did not adversely affect the growth, viability, or morphological development of the offspring. As a result, the developmental toxicity in this study was $\geq$ 40 mg/kg/day; the LOAEL could not be determined at the doses

evaluated. Maternal toxic effects at 30 and 40 mg/kg/day were minor and transient; therefore, the evidence of toxicity was equivocal. However, a slightly higher dose of 50 mg/kg/day was found to be excessively toxic, resulting in maternal morbidity and mortality. Evaluation of developmental toxicity at doses above 40 mg/kg/day was precluded by excessive maternal toxicity.

BZM has not been tested for developmental toxicity. However, due to its close structural similarity to PHM, as well as the demonstrated higher level of acute toxicity of PHM, it would be expected that BZM would be of a similar order of magnitude as PHM, if not of lower developmental toxicity.

Summary: Data for the structural surrogate PHM can be used as read-across data for BZM, and no further testing of BZM is warranted for this endpoint (see Table 5 and IUCLID Documents).

Mammalian Toxicity Summary: Sufficient mammalian toxicity data exist for BZM and PHM for all SIDS Mammalian Toxicity Endpoints except repeated dose and genetic toxicity. Additional testing (OECD Guidelines 407 and 473) is proposed to fulfill these two SIDS endpoints.

VIII. "BEYOND SIDS" ENDPOINTS:

Studies have been performed to investigate skin irritation and skin sensitization potential (see IUCLID document).

IX. CONCLUSIONS

As summarized below, CPChem concludes that there are sufficient, reliable data on BZM and its structural surrogate, PHM, for many of the SIDS endpoints following a thorough review of company proprietary files, the peer-reviewed literature, and/or calculations using widely accepted computer modeling programs.

- **PHYSICOCHEMICAL DATA**. Physicochemical endpoints for BZM are fulfilled by using existing measured data or data calculated by the EPIWIN© computer model. No additional testing is proposed.

- **ENVIRONMENTAL FATE**. Sufficient data are available to characterize environmental fate endpoints, with the exception of hydrolysis, for BZM. An estimation from a Level III fugacity model predicts that both BZM, as well as its structural surrogate PHM, will likely partition to soil and water. Ready biodegradation testing showed that BZM is not readily biodegradable and the predicted bioconcentration factors and organic carbon partition coefficients for BZM and PHM suggest similar fate profiles in the environment and a slight

bioaccumulation hazard for either BZM or PHM. Additional testing for the hydrolysis endpoint is proposed.

- **ACUTE AQUATIC TOXICITY**. Only limited acute aquatic toxicity data are available for BZM and PHM. Additional acute toxicity testing for fish and aquatic plants is proposed for BZM.

- **ACUTE MAMMALIAN TOXICITY**. Mammalian toxicity data demonstrates a low order of toxicity via oral, dermal, and inhalation routes of exposure. Sufficient data are available to fulfill the acute toxicity endpoint for BZM and no additional testing is proposed.

- **GENETIC TOXICITY**. Limited genetic toxicity data is available for BZM. Additional testing using an *in vitro* chromosomal aberration assay is proposed.

- **REPEATED DOSE TOXICITY**. No repeated dose toxicity testing data for BZM or PHM was identified. Additional testing for this endpoint is proposed.

- **REPRODUCTIVE AND DEVELOPMENTAL TOXICITY**. BZM has not been tested for reproductive and developmental toxicity, but, due to its close structural similarity to PHM, it would be expected to be of a similar order of magnitude as PHM. Given that PHM is characterized for this endpoint and is expected to produce results of the same order of magnitude, PHM can be used as a structural surrogate for BZM, and no further BZM testing is warranted for this endpoint.

Test Plan Summary: Additional testing with BZM is proposed to fulfill the following five endpoints:

- **Hydrolysis (OECD 111);**
- **Acute Toxicity to Fish (OECD 203);**
- **Acute Toxicity to Aquatic Plants (OECD 201);**
- **Repeated Dose (OECD 407); and**
- **Genetic Toxicity: *In vitro* Mammalian Cytogenetic Test (OECD 473).**

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